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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,542	11/15/2001	Avi J. Ashkenazi	P2730P1C26	7269

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BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610

EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,542	GENENTECH, INC.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-121 and 123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-121 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment dated 6/4/04 has been entered into the record.

B. Claims 119-124 were pending in this application. In the Amendment dated 6/4/04 Applicants canceled claims 122 and 124. Therefore, claims 119-121 and 123 are pending and are the subject of this Office Action.

C. The Information Disclosure Statement dated 6/4/04 has been entered into the record. All references have been considered.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Priority

A. The present invention continues to receive priority only to the filing date of the instant invention, 11/15/01. Applicants argue that the gene amplification assay is sufficient to establish a patentable utility of the instant invention, which was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, priority to which has been claimed in this application. Hence, the present application is entitled to at least the priority date of June 23, 1999. This argument has been considered, but is not deemed persuasive since the claims remain rejected under 35 USC 101 as seen below.

3. Specification

A. The objection to the specification has been withdrawn in view of Applicants' amendments to remove all embedded hyperlinks and/or other forms of browser-executable code.

B. The objection to the specification has been withdrawn in view of Applicants' amendment to the title to recite "PRO1281 antibodies," the claimed subject matter.

4. Claim Objections

A. The objection to claim 119 has been withdrawn in view of Applicants' amendment to remove "shown in Figure 233" with "of."

B. Claim 119 is objected to since the parentheses around "SEQ ID NO:326" should be removed.

5. Claim Rejections - 35 USC § 101

A. Claims 119-121 and 123 remain rejected under 35 USC 101 for the reasons already of record on pages 3-4 of the Office Action dated 3/9/04. Applicants state that, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Applicants further state that, under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed and that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. Applicants also state that if the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, then a rejection based on utility should not be imposed. The Examiner is not questioning that the present invention is not credible. The issue of "specific" and "substantial" will be discussed below.

Turning to Applicants' arguments, Applicants are relying on the gene amplification data for patentable utility (e.g. specific and substantial) for this case. They argue that gene amplification is an essential mechanism for oncogene activation and the assay is well-described in Example 170, page 539 of the present application. The gene amplification data shows that genomic DNA was isolated from a variety of primary cancers and cancer cell lines listed in Table 9 (especially page 554, Table 9C) which includes primary colon cancers of the type and stage indicated in Table 8 (page 546).

These arguments have been considered, but are not deemed persuasive. The present claims are drawn to antibodies which bind PRO1281 whereas these arguments are drawn to genomic DNA which, ultimately, encodes PRO1281. The fact that gene amplification may be an essential mechanism for oncogene activation is, respectfully, not relevant to the present claims which, again, are drawn to antibodies. The fact that genomic DNA was isolated from a variety of cancers does not provide a utility for the antibodies which bind the protein encoded by the DNA since Applicants have not demonstrated that the increase in genomic DNA would ultimately lead to an increase in protein expression in these cancer cells, which would be required in order for the antibodies of the present invention to have a utility in identifying these cells.

Applicants argue that it is generally well-understood in the art that DNA copy number influences gene expression and cite Orntoft et al., Hyman et al. and Pollack et al. as supporting reference. Applicants submit a Declarations by Dr. Polakis. This Declaration states that, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor

cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. Therefore, Applicants argue that, given the combined tcachings in the art exemplified by Orntoft et al., Hyman et al. and Pollack et al., as well as the Polakis Declaration, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO1281 gene, that the PRO1281 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1281 proteins and nucleic acids have utility in the diagnosis of cancer. Applicants also argue that Hanna and Mornin teach that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma and that the diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by 1HC).

These arguments, including the Declaration by Dr. Polakis, have been considered, but are not deemed persuasive. First, the Examiner's position that an increase in nucleic acid copy number is not predictive of a similar association for protein is supported by the prior art. Therefore, the art does not convincingly recognize that protein levels are increased when gene amplification occurs. For example, Pennica et al., teach that WISP1 and WISP2 are both amplified in tumors, but RNA expression of WISP2 was *reduced* in 79% of tumors, while that of WISP1 was *increased* in 84% of tumors (see abstract). See also Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Finally, see Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that gene amplification, or increased transcription, results in increased protein levels. Accordingly, the showing that

the DNA encoding PRO1281 is present in increased copy number in a particular tumor type is not sufficient to establish any utility for the protein encoded thereby or antibody that binds to the protein. Regarding Hanna and Mornin, they teach the HER-2/neu gene, which has not been shown to be PRO1281. In view of the prior art presented by the Examiner, the data taught by Hanna and Mornin is not persuasive since it difficult to extrapolate data from one protein to another.

Applicants further argue that, according to the Declaration by Dr. Ashkenazi, "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment." The Declaration further states that "parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy...crucial information for the practicing clinician."

These arguments, including the Declaration by Dr. Ashkenazi, have been considered, but are not deemed persuasive. It is well-known in the art that most genes are not amplified in cancer cells and are not used as markers. The fact that a particular gene is not amplified, in the absence of further supporting evidence from Applicants, does not provide a specific and substantial utility for that DNA. All it demonstrates is that DNA is not involved in that cancer. Similarly, the argument that these genes may enable more accurate tumor classification is also not persuasive, as Applicants have not demonstrated how the genomic DNA for PRO1281 fits into this equation, (i.e. what specific and substantial information it will provide). Any genomic DNA can be used for this purpose since all DNA levels will either increase, decrease, or remain the same. Therefore, in the absence of further information regarding PRO1281, the idea that DNA levels may remain constant does not provide a specific or substantial utility. In addition, while the entire wealth of information regarding gene amplification as a whole may be useful, a single genomic DNA, such as the one disclosed in this invention for PRO1281, by itself, is not. **Regardless, the claims are drawn to the antibody, not the DNA**. Even, *arguendo*, mRNA expression was correlated to PRO1281 gene amplification, or that this DNA could somehow enable more accurate tumor classification does still not provide a utility for the antibody to PRO1281 since no information regarding altered expression of PRO1281 is disclosed in the specification. Finally, a cell in which the gene did not amplify (i.e. "absence of gene product over-expression") would be expected to have the same protein expression as non-cancerous cells. Therefore, the antibody would show the same specific binding to cancerous and non-cancerous cells. For this reason, there would be no utility for the antibody in the detection of cancer since this antibody could not be used to distinguish between cancerous and non-cancerous cells.

6. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 119-121 and 123 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 4 of the Office Action dated 3/9/04 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

7. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, have been withdrawn in view of Applicants' cancellation of claims 122 and 124 and the incorporation of the limitations of claim 122 into claim 119.

8. Claim Rejections - 35 USC § 102

A. Claims 119-121 and 123 remain rejected under 35 USC 102 as being anticipated by Baker et al. (WO 99/63088) for the reasons already of record on page 5 of the Office Action dated 3/9/04. Applicants argue that the rejection should be withdrawn since they are entitled to a priority date of June 23, 1999, which predates the Baker et al. reference. This argument has been considered, but is not deemed persuasive since Applicants are not receiving priority to June 23, 1999, for the reasons discussed in the above rejection under 35 USC 101 and in the section of this Office Action entitled "Priority." Therefore, the priority date remains the filing date of the present invention, 11/15/01.

B. Claims 119-121 and 123 remain rejected under 35 USC 102 as being anticipated by Tang et al. (WO 01/53312) for the reasons already of record on page 5 of the Office Action dated 3/9/04. Applicants argue that the rejection should be withdrawn since they are entitled to a priority date of June 23, 1999, which predates the Tang et al. reference. This argument has been considered, but is not deemed persuasive since Applicants are not receiving priority to June 23, 1999, for the reasons discussed in the above rejection under 35 USC 101 and in the section of this Office Action entitled "Priority." Therefore, the priority date remains the filing date of the present invention, 11/15/01.

9. Claim Rejections - 35 USC § 103

A. Claims 119-121 and 123 remain rejected under 35 USC 103 as being unpatentable over Weimann (2001) in view of Baker et al. (WO 99/63088) for the reasons already of record on pages 5-6 of the Office Action dated 3/9/04. Applicants argue that the rejection should be withdrawn since they are entitled to a priority date of June 23, 1999, which predates the Weimann and Baker et al. references. This argument has been considered, but is not deemed persuasive since Applicants are not receiving priority to June 23, 1999, for the reasons discussed in the above rejection under 35 USC 101 and in the section of this Office Action entitled "Priority." Therefore, the priority date remains the filing date of the present invention, 11/15/01.

B. Claims 119-121 and 123 remain rejected under 35 USC 103 as being unpatentable over Weimann (2001) in view of Tang et al. (WO 01/53312) for the reasons already of record on page 6 of the Office Action dated 3/9/04. Applicants argue that the rejection should be withdrawn since they are entitled to a priority date of June 23, 1999, which predates the Weimann and Tang et al. references. This argument has been considered, but is not deemed persuasive since Applicants are not receiving priority to June 23, 1999, for the reasons discussed in the above rejection under 35 USC 101 and in the section of this Office Action entitled "Priority." Therefore, the priority date remains the filing date of the present invention, 11/15/01.

10. Conclusion

A. No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (571) 272-0887.

Official papers filed by fax should be directed to (703) 872-9306. Fax draft or informal communications with the examiner should be directed to (571) 273-0888.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-0700.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
June 24, 2004

ROBERT LANDSMAN
PATENT EXAMINER